HIGH PURITY BRANCHED ALKYLSILSESQUIOXANE FLUIDS

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The invention provides high purity branched alkylsilsesquioxane containing fluids of the general formula Me3SiO-(Me3SiORSiO)x-SiMe3, wherein Me is methyl, R is a monovalent hydrocarbon substituent, and x is 1 to 6, and an essentially zero waste process for their synthesis in quantitative yield; and especially n-octylsilsesquioxane containing fluids which are structural analogs of phenylsilsesquioxane containing fluids of the general formula Me3SiO-(Me3SiOPhSiO)x-SiMe3, wherein Me is methyl, Ph is phenyl, x is 1 to 6, and have substantially identical sensory properties to their phenylsilsesquioxane counterparts.

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(57) Abstract

The present invention provides greater than 99 % pure bis(triorganosilyl)hydroxycarboxylates of the general formulae: $R_3SiO–CHR^1–COO–SiR_3$ and $R_3SiO–CHR^1–R^2COO–SiR_3$ wherein each R is independently a monovalent straight or branched chain alkyl or alkenyl group having from 1 to about 6 carbon atoms, or an aryl group, R^1 may be hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, or an aryl group, and R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms; a process for producing the bis(trimethylsilyl)–hydroxycarboxylates comprising the trimethylsilylation with hexamethyldisilazane of the corresponding hydroxy carboxylic acids; cosmetic formulation comprising the greater than 99 % pure bis(trimethylsilyl)hydroxycarboxylates dissolved in aprotic media; and a method of delivering hydroxycarbxylic acids to the epidermis without apparent irritation or inflammation of the epidermis or stratum corneum.

NOVEL DELIVERY OF HYDROXY CARBOXYLIC ACIDS

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation-in-part application of United States Application Serial No.: 09/041,173, filed March 12, 1998.

FIELD OF THE INVENTION

The present invention relates to high purity bis (triorganosilyl)hydroxycarboxylic acid derivatives and a method for their preparation. More specifically, the present invention relates to more than 99% pure bis (triorganosilyl)-hydroxycarboxylic acid derivatives prepared by triorgano-silylation of hydroxycarboxylic acids by hexaorganodisilazanes. The present invention also relates to non-irritating cosmetic formulations comprising bis (triorganosilyl)hydroxycarboxylic acid derivatives.

BACKGROUND OF THE PRESENT INVENTION

There is considerable prior art relating to the use of hydroxycarboxylic acids, in particular alpha-hydroxy-carboxylic acids such as glycolic acid and lactic acid, in skin care applications. Alpha-hydroxycarboxylic acids are basically used as chemical versions of facial scrubs. When applied topically, they accelerate the sloughing off of dead cells from the outer layer of the skin, the stratum corneum, forcing the underlying cells in the epidermis to accelerate the creation of fresh new cells to replace them. The body may also attempt to repair this minor damage, by depositing new collagen in the underlying dermal layer. The net apparent result is smoother, firmer, more evenly pigmented skin reminiscent of the person's skin at an earlier time chronologically. See generally, web page found at http://www.thriveonline.com/@@62AH9wYA2@Hgbb2a/thrive/-health/skinsave.intro.html (July 9, 1997 11:29 AM).

There are known side effects associated with the use, and in particular the prolonged use, of alpha-hydroxycarboxylic acids. These include acute skin irritation on application of the alpha-hydroxycarboxylic acid with

possible development over time of an allergic-like reaction to such applications with some patients, and increased sun sensitivity.

Various techniques have been employed to decrease the side effects of alpha-hydroxycarboxylic acids such as partial neutralization, which increases the pH of the applied product (see Market View, The U.S. Cosmetics Industry, "Special Report, AHA Consumer Products 1990-1993," p.6.); partial or complete esterification, which also increases the pH of the applied product (see Genetic Engineering News dated April 1, 1996 found at http://www.dc.enews.com/magazines/geng_news/archive/960401-005.html on July 9, 1997); or the use of additives (see, Hahn, "A New Line of Defense Against Aging: Breaking the Irritation Barrier," DCI, January 1998). See also, generally, Parab, United States Patent No. 5,420,105; Habif et al., United States Patent No. 5,690,947; Hahn et al., United States Patent No. 5,716,625; De Lacharriere et al., United States Patent No. 5,714,155. None of these approaches change the real interaction of the alpha-hydroxycarboxylic acid with the epidermis. Rather, they provide the appearance of irritation reduction.

None of the current "solutions" to the irritation problem of alpha-hydroxycarboxylic acids has approached the problem by changing the delivery mechanism of the active ingredient such that it does not irritate the outer layers of the skin, yet the active ingredient targets the lipid-rich layers of the skin, more efficiently delivering free alpha-hydroxy-carboxylic acid to those sites in the epidermis where the new cells are created.

Alpha-hydroxycarboxylic acid derivatives which have the ability to efficiently deliver free alpha-hydroxycarboxylic acids to preferred sites in the epidermis to promote new cell and collagen growth without irritation of the skin and with no associated toxicity concerns have clearly been sought for years to no avail. Associated with such a

material would also be the desire for a simple high yield manufacturing process to make the material in the very high purity normally associated with cosmetic ingredients.

BRIEF DESCRIPTION OF THE DRAWINGS

The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

FIGURE 1 is a colored graphical depiction which shows the results of applying a lotion of the present invention in accordance with Example 7 to a 36 year old female patient who participated in the study of Example 7.

SUMMARY OF THE INVENTION

The present invention provides greater than 99% pure bis(triorganosilyl)hydroxy carboxylic acid derivatives of the general formulae:

$$R_3SiO\text{-}CHR^1\text{-}COO\text{-}SiR_3$$

$$R_3SiO\text{-}CHR^1\text{-}R^2COO\text{-}SiR_3$$

wherein each R is independently a monovalent straight or branched chain alkyl or alkenyl group having from 1 to about 6 carbon atoms, or an aryl group, R^1 may be hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, or an aryl group, and R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms. The yield of bis(triorganosilyl)-hydroxy carboxylic acid derivatives prepared by the method of the present invention is greater than about 95%.

The present invention also provides a simple method for rapidly producing bis(triorganosilyl)hydroxycarboxylic acid derivatives of the general formulae:

$$R_3SiO\text{-}CHR^1\text{-}COO\text{-}SiR_3$$

$$R_3SiO\text{-}CHR^1\text{-}R^2COO\text{-}SiR_3$$

wherein each R is independently a monovalent straight or branched chain alkyl or alkenyl group having from 1 to about

6 carbon atoms, or an aryl group, R^1 may be hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, or an aryl group, and R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms, the method comprising triorganosilylation with a hexaorganodisilazane of the corresponding hydroxy carboxylic acids of the general formulae:

$$HO\text{-}CHR^1\text{-}COOH$$

$$HO\text{-}CHR^1\text{-}R^2COOH$$

wherein R^1 may be hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, or an aryl group, and R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms.

It has been found that bis(triorganosilyl)hydroxycarboxylate materials, which are aprotic, can be readily dissolved in typical aprotic solvents including organosilicone materials and can be delivered to the skin even under repeat insult conditions with no apparent irritation even under chronic use.

It is well known to those skilled in the art, that organosilicon chemicals containing silylether, Si-O-C, linkages and silylester, Si-O-C=O, linkages are hydrolytically unstable. In particular, silylester linkages are known to those skilled in the art to be more hydrolytically unstable than silylethers. Accordingly, bis(triorganosilyl)hydroxycarboxylates, on exposure to moisture, will undergo hydrolysis forming initially triorganosilylhydroxycarboxylic acids as per Equation 1.

$$R_3SiOCHR^1COOSiR_3 + H2O \longrightarrow R_3SiOCHR^1COOH + R_3SiOH \quad (1)$$

Hydrolysis of both silylethers and silylesters is catalyzed

by either acids or bases, thus although bis(triorganosilyl)-hydroxy carboxylates are neutral, as they begin to hydrolyze they form carboxylic acids which catalyze further hydrolysis. Thus, the hydrolysis process is auto-catalytic. The second step of the hydrolysis process liberates free hydroxycarboxylic acid as per Equation 2.

$$R_3SiOCHR^1COOH + H2O \longrightarrow HOCHR^1COOH + R_3SiOH \quad (2)$$

Bis(triorganosilyl)hydroxycarboxylates of the general formulae:

$$R_3SiO\text{-}CHR^1\text{-}COO\text{-}SiR_3$$
$$R_3SiO\text{-}CHR^1\text{-}R^2COO\text{-}SiR_3$$

wherein each R is independently a monovalent straight or branched chain alkyl or alkenyl group having from 1 to about 6 carbon atoms, or an aryl group, R^1 may be hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, or an aryl group, and R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms, have the ability to deliver hydroxycarboxylic acids to the skin in such a manner as to not cause irritation or inflammation either acutely or chronically.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides greater than 99% pure bis(triorganosilyl)hydroxycarboxylic acid derivatives of the general formulae:

$$R_3SiO\text{-}CHR^1\text{-}COO\text{-}SiR_3$$
$$R_3SiO\text{-}CHR^1\text{-}R^2COO\text{-}SiR_3$$

wherein each R is independently a monovalent straight or branched chain alkyl or alkenyl group having from 1 to about 6 carbon atoms, or an aryl group, R^1 may be hydrogen, a monovalent straight or branched chain alkyl

group having from 1 to about 18 carbon atoms, or an aryl group, and R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms.

The bis(triorganosilyl)hydroxy carboxylic acid derivatives of the present invention are prepared by triorganosilylation with a hexaorganodisilazane of the corresponding hydroxy carboxylic acids of the general formulae:

$$HO\text{-}CHR^1\text{-}COOH$$

$$HO\text{-}CHR^1\text{-}R^2COOH$$

wherein R^1 may be hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, or an aryl group, and R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms.

Hydroxycarboxylic acids suitable for use in the process of the present invention, and methods for their preparation are well known to those skilled in the art. Specific examples include, but are not limited to, alpha-hydroxycarboxylic acids including glycolic acid and lactic acid, and beta-hydroxy- carboxylic acids including salicylic acid. The preferred hydroxy carboxylic acid is lactic acid.

Hexaorganodisilazanes suitable for use in the process of the present invention, and methods for their preparation are well known to those skilled in the art. Specific examples include, but are not limited to hexamethyldisilazane, hexaethyldisilazane, 1,3-divinyltetramethyldisilazane, and 1,3-diethyltetramethyldisilazane. The preferred hexaorganodisilazane is hexamethyldisilazane.

The triorganosilylation reaction may be carried out at temperatures ranging from about 40°C to about 125°C,

preferably between about 60°C and about 95°C.

The compositions of the present invention are useful for all known utilities for topical administration of hydroxycarboxylic acids such as α-hydroxy acids and ß-hydroxy acids. These include, for example, treatment of dry skin, xerosis, ichthyosis, dandruff, acne, keratoses, psoriasis, wrinkles, warts, blemished skin, hyperpigmented skin, inflammatory dermatoses, eczema, pruritis, hyperkerotic skin, lentigines, melasma, age spots, laxity, leathery texture, roughness, sallow complexion, scaling, telangiectasia, mottled pigmentation, skin atrophy caused by steroids and skin changes associated with intrinsic aging and photodamage.

In addition to the compositions of the present invention, the cosmetic formulations of the present invention may contain any of a large number of additional cosmetic and pharmaceutical agents, provided that such additional agents are inert with respect to formation, stability and activity of the compositions of the present invention, i.e., they are reaction inert. Additionally any such additives must be aprotic.

Cosmetic and pharmaceutical agents useful in the practice of the present invention include those that improve or eradicate age spots, keratoses and wrinkles, analgesics, anesthetics, antiacne agents, antibacterials, antiyeast agents, antifungal agents, antiviral agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antiperspirants, antipsoriatic agents, antiseborrheic agents, hair conditioners, hair treatment agents, antiaging and antiwrinkile agents, antiphotoaging agents, antiasthmatic agents and bronchodilators, sunscreen agents, antihistamine agents, skin lightening agents, depigmenting agents, vitamins, corticosteroids, tanning agents, hormones, retinoids and topical cardiovascular agents.

The cosmetic formulation may be in the form that any aprotic formulation may take, including but not limited to lotions, creams, gels, sticks, ointments, liposomes, aerosols, polymeric gels, plasters, patches, films or tapes, the preparation of which are well known to those skilled in the art.

A neat bis(triorganosilyl)lactate can be applied to the skin with significantly less injury to the stratum corneum and epidermis than application of lactic acid at a similar aqueous concentration. Solutions of bis(triorganosilyl)lactate in aprotic vehicles at 10% effective lactic acid concentration (after hydrolysis), in the form of lotions or ointments, can be applied to the skin with no apparent acute or chronic irritation or inflammation.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate the present invention. They are not to be construed to limit the scope of the appended claims in any manner whatsoever.

EXAMPLE 1

In a 3 litre 3-neck RB flask equipped with a magnetic stirring bar, a thermometer well and thermometer, addition funnel and heating mantle was placed 510 g (4.72 mole) of a 1:1 molar ratio of 83 % wt/wt lactic acid in water. This liquid was heated and stirred to 60°C. To the addition funnel was added 1811 g (11.24 mole) of hexamethyldisilazane and the system was blanketed with a dry nitrogen atmosphere. Hexamethyldisilazane was then added slowly with stirring from the addition funnel to the lactic acid in water mixture, maintaining the temperature of the mixture at 60°C. Ammonia was liberated from the reaction medium and allowed to escape from the system through a bubbler. The addition of hexamethyldisilazane was continued overnight. After complete addition of the hexamethyldisilazane the mixture in the RB flask was heated at 80°C for 4 more hours to ensure that the

reaction had been driven to completion. A GC analysis of the crude product at this point showed the presence of three materials, hexamethyldisiloxane, hexamethyldisilazane and bis(trimethylsilyl)lactate in the approximate ratio of 35:15:50 respectively. The crude product was then fractionated producing 700 g (92% theory) of hexamethyldisiloxane, 95 g of a mixture of hexamethyldisiloxane and hexamethyldisilazane, 260 g (90% theory) of unreacted hexamethyldisilazane. At this point the remaining liquid was cooled to room temperature, a full vacuum was applied and the product was distilled at 1 mm of Hg pressure at a temperature of 40°C to provide 1050 g (95% yield) of >99.9% pure (by GC analysis) clear, colorless and odorless bis(trimethylsilyl)lactate, refractive index 1.4053 (21°C) and density 0.896 (21°C). A GC/MS analysis of this material identified the molecular weight of the chemical to be 234.

EXAMPLE 2

In a 250 ml 3-neck RB flask equipped with a magnetic stirring bar, a thermometer well and thermometer, a powder addition funnel and heating mantle was placed 106 g (0.66 mole) of hexamethyldisilazane. This liquid was heated and stirred to 60°C. To the powder addition funnel was added 45 g (0.59 mole) of solid glycolic acid and the system was blanketed with a dry nitrogen atmosphere. Solid glycolic acid was then added slowly with stirring from the addition funnel to the hexamethyldisilazane, maintaining the temperature of the mixture at 60°C. Ammonia was liberated from the reaction medium and allowed to escape from the system through a bubbler. The addition was completed in 4 hours. After complete addition of the glycolic acid the mixture in the RB flask was heated at 80°C for 4 more hours to ensure that the reaction had been driven to completion. A GC analysis of the crude product at this point showed the presence of two materials, hexamethyldisilazane and bis(trimethylsilyl)glycolate in the

approximate ratio of 10:90 respectively. The crude product was then stripped to remove the excess hexamethyldisilazane leaving the product which was distilled at a temperature of 45°C at a vacuum of 1 mm of Hg to provide 120 g (95% yield) of 100% pure (by GC analysis) clear, colorless and odorless bis(trimethylsilyl)glycolate, refractive index 1.4119 (21°C) and density 0.905 (21°C). A GC/MS analysis of this material identified the molecular weight of the chemical to be 220.

EXAMPLE 3

In a 250 ml 3-neck RB flask equipped with a magnetic stirring bar, a thermometer well and thermometer, a powder addition funnel and heating mantle was placed 59 g (0.37 mole) of hexamethyldisilazane. This liquid was heated and stirred to 60°C. To the powder addition funnel was added 45 g (0.29 mole) of solid salicylic acid and the system was blanketed with a dry nitrogen atmosphere. Solid salicylic acid was then added slowly with stirring from the addition funnel to the hexamethyldisilazane, maintaining the temperature of the mixture at 60°C. Ammonia was liberated from the reaction medium and allowed to escape from the system through a bubbler. The addition was completed in 4 hours. After complete addition of the salicylic acid the mixture in the RB flask was heated at 80°C for 4 more hours to ensure that the reaction had been driven to completion. A GC analysis of the crude product at this point showed the presence of two materials, hexamethyldisilazane and bis(trimethylsilyl)salicylate in the approximate ratio of 25:75 respectively. The crude product was then stripped to remove the excess hexamethyldisilazane leaving the product which was distilled at a temperature of 78°C at a vacuum of 1 mm of Hg to provide 77 g (95% yield) of 100% pure (by GC analysis) clear, colorless and odorless bis(trimethylsilyl)salicylate, refractive index 1.4788 (21°C) and density 0.99 (21°C). A GC/MS analysis of this material

identified the molecular weight of the chemical to be 282.

EXAMPLE 4

Primary skin irritation studies in rabbits of undiluted bis(trimethylsilyl)lactate was evaluated by Hill Top Research, Inc. (Project No. 97-8487-21) in compliance with the conditions specified in the regulation for the enforcement of the Federal Hazardous Substances Act (16 C.F.R. § 1500). The test material produced moderate to severe erythema and severe edema (raised more than 1 mm and extending beyond the area of exposure) when applied to one intact and one abraded skin site on each of six rabbits. Additional changes noted in the coloration or texture of the skin included purple, light brown, green and green-brown discoloration on and extending beyond sites; in-depth blanching on site; blanching on and extending beyond site; and site and areas beyond site coriaceous. The Primary Irritation Index (PII) was found to be 7.1 based upon erythema and edema. Evidence of corrosion (in-depth blanching) was noted at an intact and abraded site at the 72 hour reading. Undiluted bis(trimethylsilyl)lactate is classified as a primary irritant but not as a corrosive based upon the response observed following dermal application.

For comparison, a solution of 85% lactic acid in water is classified as corrosive and causes burns. Suitable protective clothing includes heavy rubber gloves and eye and face protection. (Reference: MSDS from Aldrich Chemical Company, Inc., P.O. Box 355, Milwaukee, WI 53201, USA)

EXAMPLE 5

Facial Sensitivity studies in humans were carried out by Hill Top Research, Inc. (Project Nos. 97-2809-72 and 100969-72). The studies followed a double-blinded paired comparison design of 10% (w/w) lactic acid in water, 25% bis(trimethylsilyl)lactate) in Phenyl Trimethicone, 25% bis-trimethylsilyl)glycolate in Phenyl Trimethicone, 20%

bis-(trimethylsilyl)salicylate in Phenyl Trimethicone, Phenyl Trimethicone and water. The objective of the studies was to compare the stinging potential of the three trimethylsilylated hydroxyacid derivatives in an anhydrous delivery vehicle to that of the standard water-based chemical probe under supervised, time application procedures. Thirty female subjects, prequalified as "stingers" to 10% lactic acid, completed the studies where the test samples were applied to the nasolabial fold. Only three of the thirty subjects demonstrated a mild sting response. There were no adverse events associated with the use of the test articles.

EXAMPLE 6

Anhydrous lotion and anhydrous ointment formulations have been developed containing 25% (w/w) bis(trimethylsilyl)lactate as the active ingredient for chronic exposure and efficacy testing. This concentration corresponds to 10% lactic acid upon exposure of the formulations to water and complete hydrolysis of the bis(trimethylsilyl)lactate.

The compositions of the formulations are as follows:

Lotion:	3-n-Hexylheptamethyltrisiloxane	50%
	Bis(trimethylsilyl)lactate	25%
	Dimethiconol (HMW)	18%
	Polybutene	4%
	Caprylyl Trimethicone	2%
	Pareth-15	0.5%
	Fragrance	0.5%
Ointment:	Bis(trimethylsilyl)lactate	25%
	C24-28 Alkylmethylsiloxane Wax	24.5%
	Caprylic/Capric/Stearic Triglycerides	25%
	3-n-Hexylheptamethyltrisiloxane	20%
	Caprylic/Capric Triglycerides	3%
	Caprylyl Trimethicone	2%
	Fragrance	0.5%

Repeat insult daily topical application to human skin

of both the lotion and the ointment was carried out for 30 days (60 applications on the inside of the forearm and on the back of the hand). No acute reactions to these formulations were observed or felt during this period and no indications of sensitization to the formulations were observed.

EXAMPLE 7

The anhydrous lotion and anhydrous ointment formulations described in Example 6 were utilized in a comprehensive efficacy testing program conducted by Hill Top Research, Inc. A lotion and an ointment containing the same ingredients as described above, except without the active, bis(trimethylsilyl)lactate were also prepared. An efficacy study of the four formulations, using over 100 women, of ages ranging from 30 to 60 years, was conducted over a 90 day period. The group was divided into approximately 35 with the active lotion, 17 with the inactive lotion, 35 with the active ointment and 17 with the inactive ointment. Participants were requested to apply their test material to the face twice daily. Visual analysis of participants was conducted at the beginning, and weeks 2, 4, 8 and 12. A trained dermatologist supervised these analyses. Silicone negative facial skin replicates were made of all participants at the beginning, and weeks 4 and 12. Quantitative analysis of the skin replicates was obtained by laser light scanning directed at a 25° angle from the plane of the replica. A Cohu Solid State B&W camera was used to photograph each of the scans. The B&W luminance pattern of each scan was then converted into a visible color image of each replica. Changes in the skin surface during the 90 day efficacy test are readily seen via these color images. Standard statistical methods were used to analyze all of the data obtained in this study.

Twenty nine within treatment study parameters and fifteen between treatment study parameters were determined

to be statistically significant. These include reductions in fine lines, coarse wrinkling, mean spacing of lines, tactile roughness, mottled pigmentation, yellowing, and erythema. Reduction in the % of the negative skin replicate area covered by shadows was statistically significant. Table I lists all of the study parameters which were identified to have undergone statistically significant change. Figure 1 shows the results in color of one of the 36 year old female patients treated with a lotion with the active ingredient.

TABLE I

Statistically Significant Study Parameter Changes

Study Parameter (Within Treatment)	
% Area Covered by Shadow	Cream w/ Active vs. Baseline at Week 4
% Area Covered by Shadow	Gel w/ Active vs. Baseline at Week 12
Fine Lines	Cream Base vs. Baseline at Weeks 2/8
Fine Lines	Cream w/ Active vs. Baseline at Weeks 2/4/8/12
Fine Lines	Gel Base vs. Baseline at Week 8
Fine Lines	Gel w/ Active vs. Baseline at Weeks 2/4/8/12
Coarse Wrinkling	Cream w/ Active vs. Baseline at Weeks 2/8/12
Coarse Wrinkling	Gel w/ Active vs. Baseline at Weeks 2/8
Normal A Roughness	Cream w/ Active vs. Baseline at Weeks 4/12
Normal A Roughness	Gel w/ Active vs. Baseline at Weeks 4/12
Normal Z Roughness	Cream w/ Active vs. Baseline at Weeks 4/12
Normal Z Roughness	Gel w/ Active vs. Baseline at Weeks 4/12
Tactile Roughness	Cream Base vs. Baseline at Week 8
Tactile Roughness	Cream w/ Active vs. Baseline at Week 8
Tactile Roughness	Gel Base vs. Baseline at Week 8
Tactile Roughness	Gel w/ Active vs. Baseline at Week 8
Erythema	Cream Base vs. Baseline at Weeks 2/4/8/12
Erythema	Cream w/ Active vs. Baseline at Weeks 2/4/8/12
Mottled Pigmentation	Cream Base vs. Baseline at Weeks 2/4/8/12
Mottled Pigmentation	Cream w/ Active vs. Baseline at Weeks 2/4/8/12
Mottled Pigmentation	Gel Base vs. Baseline at Weeks 2/4/8/12
Mottled Pigmentation	Gel w/ Active vs. Baseline at Weeks 2/4/8/12
Yellowing	Cream Base vs. Baseline at Weeks 2/4/8/12
Yellowing	Cream w/ Active vs. Baseline at Weeks 2/4/8/12
Yellowing	Gel Base vs. Baseline at Weeks 2/4/8/12
Yellowing	Gel w/ Active vs. Baseline at Weeks 2/4/8/12
Stinging	Cream w/ Active vs. Baseline at Week 2 only
Stinging	Gel w/ Active vs. Baseline at Week 2 only
Study Parameter (Between Treatments)	
% Area Covered by Shadow	Cream w/ Active vs. Cream Base
Fine Lines	Cream w/ Active vs. Cream Base at Weeks 8/12
Fine Lines	Gel w/ Active vs. Gel Base at Weeks 8/12
Coarse Wrinkling	Cream w/ Active vs. Cream Base at Weeks 8/12
Coarse Wrinkling	Gel w/ Active vs. Gel Base Overall
Coarse Wrinkling	Cream w/ Active vs. Gel w/ Active Overall
Mean Wrinkle Spacing	Gel w/ Active vs. Gel Base at Week 4
Tactile Roughness	Cream w/ Active vs. Cream Base Overall
Tactile Roughness	Gel w/ Active vs. Gel Base Overall
Erythema	Cream w/ Active vs. Cream Base Overall

Erythema	Gel w/ Active vs. Gel Base Overall
Mottled Pigmentation	Cream w/ Active vs. Gel w/ Active Overall
Yellowing	Cream w/ Active vs. Cream Base Overall
Yellowing	Gel w/ Active vs. Gel Base Overall
Stinging	Gel w/ Active vs. Gel Base at Week 2 only

Variations of the present invention will suggest themselves to those skilled in the art in light of the above detailed description. For example, a mixture of hydroxy carboxylic acids could be triorganosilylated to produce a mixture of Bis (triorganosilyl)hydroxycarboxylic acid derivatives. Similarly, a mixture of hexaorganodisilazanes can be used to produce a mixture of bis(triorganosilyl)-hydroxycarboxylic acid derivatives. All such modifications are within the full intended scope of the appended claims.

All of the above-referenced patents and publications are hereby incorporated by reference.

CLAIMS

1. A cosmetic formulation comprising a bis(triorganosilyl)hydroxycarboxylate and an aprotic media.

2. A cosmetic formulation as defined in Claim 1 wherein said bis(triorganosilyl)hydroxycarboxylate comprises a compound of the general formulae

$$R_3SiO\text{-}CHR^1\text{-}COO\text{-}SiR_3$$

$$R_3SiO\text{-}CHR^1\text{-}R^2COO\text{-}SiR_3$$

wherein each R is independently a monovalent straight or branched chain alkyl or alkenyl group having from 1 to about 6 carbon atoms, or an aryl group, R^1 is hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, or an aryl group, R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms.

3. A cosmetic formulation as defined in Claim 2 wherein said bis(triorganosilyl)hydroxycarboxylate is selected from the group consisting of bis(trimethylsilyl)-glycolate, bis(trimethylsilyl)lactate, bis(trimethylsilyl)-salicylate and mixtures of any of the foregoing.

4. A cosmetic formulation as defined in Claim 2 wherein said bis(triorganosilyl)hydroxycarboxylate is at least about 99% pure.

5. A cosmetic formulation as defined in Claim 1 wherein said aprotic media is selected from the group consisting of dimethicones, cyclomethicones, alkyl methicones, alkyl dimethicones, alkyl trimethicones, aryl trimethicones, polybutenes, acyl triglycerides and mixtures of any of the foregoing.

6. A cosmetic formulation as defined in Claim 1 wherein said bis(triorganosilyl)hydroxycarboxylate is dissolved in said aprotic media at from about 10 to about

40% (w/w).

7. A method of delivering a hydroxycarboxylic acid to the epidermis without apparent corrosion or burning of the epidermis or stratum corneum, said method comprising applying a cosmetic formulation comprising a bis(triogranosilyl)-hydroxycarboxylate in an aprotic media to the epidermis.

8. A method as defined in Claim 7 wherein statistically significant reductions of one or more of fine lines, coarse wrinkling, roughness, erythema, mottled pigmentation and yellowing are obtained within a twelve week period.

9. A method as defined in Claim 7 wherein said bis(triorganosilyl)hydroxycarboxylate comprises a compound of the general formulae

$$R_3SiO\text{-}CHR^1\text{-}COO\text{-}SiR_3$$

$$R_3SiO\text{-}CHR^1\text{-}R^2COO\text{-}SiR_3$$

wherein each R is independently a monovalent straight or branched chain alkyl or alkenyl group having from 1 to about 6 carbon atoms, or an aryl group, R^1 is hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, or an aryl group, R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms.

10. A method as defined in Claim 9 wherein said bis(triorganosilyl)hydroxycarboxylate is selected from the group consisting of bis(trimethylsilyl)-glycolate, bis(trimethylsilyl)lactate, bis(trimethylsilyl)-salicylate and mixtures of any of the foregoing.

11. A method as defined in Claim 9 wherein said bis(triorganosilyl)hydroxycarboxylate is at least about 99% pure.

12. A method as defined in Claim 7 wherein said aprotic media is selected from the group consisting of

dimethicones, cyclomethicones, alkyl methicones, alkyl dimethicones, alkyl trimethicones, aryl trimethicones, polybutenes, acyl triglycerides and mixtures of any of the foregoing.

13. A method as defined in Claim 7 wherein said bis(triorganosilyl)hydroxycarboxylate is dissolved in said aprotic media at from about 10 to about 40% (w/w).

14. A method as defined in Claim 13 wherein said bis(triorganosilyl)hydroxycarboxylate is dissolved in said aprotic media at about 25% (w/w).

15. A method as defined in Claim 9 wherein said hydroxycarboxylic acid is of the general formulae:

$$HO\text{-}CHR^1\text{-}COOH$$

$$HO\text{-}CHR^1\text{-}R^2COOH$$

wherein R^1 is hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, or an aryl group, and R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms.

16. A process for the preparation of greater than 99% pure bis(triorganosilyl)hydroxycarboxylates, said process comprising reacting free hydroxycarboxylic acids or their hydrates with hexaorganodisilazanes.

17. A process as defined in Claim 16 wherein said hydroxycarboxylic acid is selected from those of the general formulae:

$$HO\text{-}CHR^1\text{-}COOH$$

$$HO\text{-}CHR^1\text{-}R^2COOH$$

wherein R^1 is hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, or an aryl group, and R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched

chain alkaryl group having from 7 to about 18 carbon atoms.

18. A process as defined in Claim 16 where said hexaorganodisilazane is selected from those of the general formula:

$$R_3SiNHSiR_3$$

wherein each R is independently a monovalent straight or branched chain alkyl or alkenyl group having from 1 to about 6 carbon atoms, or an aryl group.

19. A process is defined in Claim 16 wherein the bis(triorganosilyl)hydroxycarboxylate, with a purity in excess of 99%, has the general formulae:

$$R_3SiO\text{-}CHR^1\text{-}COO\text{-}SiR_3$$

$$R_3SiO\text{-}CHR^1\text{-}R^2COO\text{-}SiR_3$$

wherein each R is independently a monovalent straight or branched chain alkyl or alkenyl group having from 1 to about 6 carbon atoms, or an aryl group, R^1 is hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, or an aryl group, and R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms, the method comprising triorganosilylation with a hexaorganodisilazane selected from those of the general formula:

$$R_3SiNHSiR_3$$

wherein each R is independently a monovalent straight or branched chain alkyl or alkenyl group having from 1 to about 6 carbon atoms, or an aryl group, of the corresponding hydroxycarboxylic acid of the general formulae:

$$HO\text{-}CHR^1\text{-}COOH$$

$$HO\text{-}CHR^1\text{-}R^2COOH$$

wherein R^1 is hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms,

or an aryl group, and R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms.

20. A process as defined in Claim 17 wherein the hydroxycarboxylic acid is selected from the group consisting of glycolic acid, lactic acid, salicylic acid and mixtures of any of the foregoing.

21. A process as defined Claim 18 wherein the hexaorganodisilazane is selected from the group consisting of hexamethyldisilazane, 1,3-diethyltetramethyldisilazane, 1,3-divinyltetramethyldisilazane, hexaethyldisilazane and mixtures of any of the foregoing.

22. A composition comprising greater than 99% pure bis(triorganosilyl)hydroxycarboxylates produced by the process as defined in Claim 16.

23. A composition as defined in Claim 22 comprising greater than 99% pure bis(triorganosilyl)hydroxy-carboxylates of the general formulae:

$$R_3SiO\text{-}CHR^1\text{-}COO\text{-}SiR_3$$

$$R_3SiO\text{-}CHR^1\text{-}R^2COO\text{-}SiR_3$$

wherein each R is independently a monovalent straight or branched chain alkyl or alkenyl group having from 1 to about 6 carbon atoms, or an aryl group, R^1 is hydrogen, a monovalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, or an aryl group, and R^2 is a divalent straight or branched chain alkyl group having from 1 to about 18 carbon atoms, an aryl group, or a straight or branched chain alkaryl group having from 7 to about 18 carbon atoms.

24. A composition as defined in Claim 23 comprising greater than 99% pure bis(trimethylsilyl)lactate, bis(trimethylsilyl)glycolate, bis(trimethylsilyl)-salicylate or mixtures of any of the foregoing.

Lotion with Active - 36 year old Female patient

After 90 day Treatment

Before Treatment

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/05200

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/695
US CL :424/472
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/472

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,229,131 A (AMIDON ET AL) 20 JULY 1993, SEE COLUMNS 9-12 OF SAME.	1-24
Y	US 5,439,689 A (HENDRICKSON ET AL) 08 AUGUST 1995, SEE COLUMNS 9-16 OF SAME.	1-24
Y	US 5,500,227 A (OSHLACK ET AL) 19 MARCH 1996, SEE COLUMNS 15-20 OF SAME.	1-24
Y	US 5,576,022 A (YANG ET AL) 19 NOVEMBER 1996, SEE COLUMNS 25-28 OF SAME.	1-24
Y	US 5,032,406 A (DANSEREAU ET AL) 16 JULY 1991, SEE ENTIRE DOCUMENT.	1-24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
27 JULY 1999	20 AUG 1999
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